Compact energy metabolism model: Brain controlled energy supply

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Outline

1 Theoretical background

2 Energy metabolism model
   Short-term model
   Long-term model

3 Conclusion

4 Outlook
Selfish brain theory

- Interdisciplinary clinical research group, University of Lübeck
- Aim: systemic understanding of the human whole-body energy metabolism.
- The brain is regarded as heavy energy consumer and as superordinate regulatory instance.
- Metabolic diseases like obesity and diabetes mellitus are explained as mistuning of energy allocation.

Mathematical modelling and life sciences

► Aim: systemic understanding of a physiological system’s behaviour.
► Models generate insight into the system behaviour.
► In-silico experiments detect critical elements to validate.

Challenges:
– enormous number of mechanisms
– mechanisms not (yet) quantified
– difficulty of experiments
– pure correlation vs. causal relation
Brain-centred energy metabolism model

- Mathematical model of the human energy metabolism regarding the brain as superior regulatory instance and as energy consumer.
- General model realistically describing the fundamental behaviour of the whole-body energy metabolism in healthy humans.
- Compact low-dimensional dynamical system.

→ ODE compartment model
Compartment model

Energy fluxes between compartments (solid) and control signals directing the energy fluxes in the organism (dashed).

Short-term energy metabolism model

**brain ATP:**
\[
\frac{d}{dt} A = p_1 \frac{G}{A} - c_1
\]

**blood glucose:**
\[
\frac{d}{dt} G = -p_1 \frac{G}{A} - p_2 GI + p_3 \frac{R}{G}
\]

**insulin:**
\[
\frac{d}{dt} I = p_4 A - p_5 I
\]

**energy resources:**
\[
\frac{d}{dt} R = p_2 GI - p_3 \frac{R}{G} + p_6 H - c_2
\]

**ingestion:**
\[
\frac{d}{dt} H = p_7 \left( f(V) - H \right)
\]

with **appetite:**
\[
V(A, G, I) = \frac{p_8}{AGI}
\]
System properties

Stationary points
The stationary point of the short-term model is unique.

Stability
On condition of a sufficiently steep ingestion activation function $f$, the short-term model features an instable stationary point implying that oscillating behaviour may occur.

B. Göbel, D. Langemann (2010), Theory Biosci
**Bifurcation analysis**

*Bifurcation parameter* $p$: steepness parameter of the ingestion activation function $f$.

At the Hopf bifurcation point $H$, a stable limit cycle (self-oscillations) branches from the stable stationary point.

Eigenvalues of the Jacobian in the stationary point for $p \in [0.001, 1]$.

In the Hopf bifurcation point $H$, a pair of complex conjugate, purely imaginary eigenvalues crosses the imaginary axis.

B. Göbel, D. Langemann (2010), Theory Biosci
Simulations

brain ATP:

blood glucose:

insulin:

resources:

ingestion:

Circadian ingestive behaviour leads to oscillating energy levels in the compartments with the typical blood glucose and insulin variations.
Long-term model

\[
\text{ingestion} : \quad \frac{d}{dt} H = p_7 \left(f(V) - H\right)
\]

- \(p_7\): sensitivity of the organism in food intake consistent with its need for energy
- \textit{Low values of } p_7: \text{ slow adaption to the body’s energy needs}
- \textit{High values of } p_7: \text{ fast adaption to the body’s energy needs}
- Short-time scale (daily): slow adaption = mild regulation
- Long-time scale (monthly): fast adaption = strong regulation
Long-term energy metabolism model

Transition $p_7 \to \infty$ leads to a description of the long-term behaviour with mean regulation of food intake:

**brain ATP:** \[
\frac{d}{dt} A = p_1 \frac{G}{A} - c_1
\]

**blood glucose:** \[
\frac{d}{dt} G = -p_1 \frac{G}{A} - p_2 G I + p_3 \frac{R}{G}
\]

**insulin:** \[
\frac{d}{dt} I = p_4 A - p_5 I
\]

**energy resources:** \[
\frac{d}{dt} R = p_2 G I - p_3 \frac{R}{G} + p_6 f(V) - c_2
\]

System properties

Stationary points
The stationary point of the long-term model is unique.

Stability
The stationary point of the long-term model is asymptotically stable under mild assumptions.

Simulations

brain ATP:

blood glucose:

insulin:

resources:

Stable long-term behaviour in accordance with homeostatic regulation of the energy metabolism.

solid: exercise
dashed: exhaustion
dash-dot: resting state
Conclusion

- The model contains the two central roles of the brain in the energy metabolism.
- Realistic description of the energy metabolism on a short time scale and on a long time scale - even with a large class of physiological interventions.
- The presented dynamical system is a step towards a systemic understanding of the human energy metabolism, and thus may shed light on defects causing metabolic diseases.
Outlook

- Extension of the model by further sub-compartments
- Interaction of the model to other regulatory systems, e.g. stress axis, memory
- Model validation
- Solution of the inverse problem to generate insight into underlying mechanisms
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